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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/008,789	11/08/2001	C. Frank Bennett	RTS-0333	4716

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EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 09/11/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Application No.	Applicant(s)	
	10/008,789	BENNETT ET AL.	
	Examiner	Art Unit	
	Terra Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 4-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Preliminary Amendment A, filed 8/27/02, in Paper No. 4 is acknowledged. Claim 3 has been canceled. Claims 1, 2 and 4-20 are pending in the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a compound 8 to 50 nucleobases in length that hybridizes with and inhibits the expression of thyroid hormone receptor interactor 6 *in vitro*, does not reasonably provide enablement for a method of inhibiting the expression of thyroid hormone receptor interactor 6 in tissues (*in vivo*) as in claim 15 or a method of treating an animal having a disease or condition associated with thyroid hormone receptor interactor 6 as in claims 16-20. The specification does not enable any person of ordinary skill in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 15-20 are drawn to or embrace an antisense-based therapy in an animal having a disease or condition associated with thyroid hormone receptor interactor 6 via a compound 8 to 50 nucleobases in length that hybridizes with and inhibits the expression of thyroid hormone receptor interactor 6.

The instant invention specification provides methodologies for antisense inhibition of thyroid hormone receptor interactor 6 in cell culture.

The specification as filed does not provide adequate guidance of examples that would show by correlation the practice of the instant invention without the need for undue trail and error experimentation. The specification as filed contemplates the therapeutic use of thyroid hormone receptor interactor 6 antisense in a broad range of diseases (e.g. hyperproliferative disorders and cancer). However, the instant specification does not show any specific link to thyroid hormone receptor interactor 6 and any specific disease such that treatment with thyroid hormone receptor interactor 6 antisense would be an apparent treatment option, without undue trial and error experimentation, for example. How does one in the art correlate the cell culture (*in vitro*) data to treat a particular disease (*in vivo*) with thyroid hormone receptor interactor 6 antisense? (i.e. this would require different modes of treatment where no specific guidance is provided for any particular disease).

The unpredictability of the art of antisense therapy in general adds to the lack of enablement for the current invention. For example, Branch (TIBS Vol. 23, February 1998) addresses the unpredictability and the problems faced in the antisense art with the following statements: "Antisense molecules and ribozymes capture the imagination with their promise or rational drug design and exquisite specificity. However, they are far more difficult to produce than was originally anticipated, and their ability to eliminate the function of a single gene has never been proven."; "To minimize unwanted non-antisense effects, investigators are searching for antisense compounds and ribozymes whose targets sites are particularly vulnerable to attack. This is a challenging quest."; "However, their unpredictability confounds research application of

nucleic acid reagents."; "Non-antisense effects are not the only impediments to rational antisense drug design. The internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules."; "Years of investigation can be required to figure out what an 'antisense' molecule is actually doing,..."; "Because knowledge of their underlying mechanism is typically acting, non-antisense effects muddy the waters."; "Because biologically active compounds generally have a variety of effects, dose-response curves are always needed to establish a compounds primary pharmacological identity. Antisense compounds are no exception. As is true of all pharmaceuticals, the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curve of conventional drugs, which typically span two to three orders of magnitude, those of antisense drugs, extend only across a narrow concentration range."; "Because it is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be determined empirically by screening large number of candidates for their ability to act inside cells."; "Binding is the rare exception rather than the rule, and antisense molecules are excluded from most complementary sites. Since accessibility cannot be predicted, rational design of antisense molecules in not possible."; and, "The relationship between accessibility to oligonucleotide (ODN) binding and vulnerability to ODN-mediated antisense inhibition *in vivo* is beginning to be explored...It is not yet clear whether *in vitro* screening techniques...will identify ODN's that are effective *in vivo*."

Jen et al. (Stem Cells, 2000, Vol. 18:307-319) discuss antisense-based therapy and the challenges that remain before the use of antisense becomes routine in a therapeutic setting. Jen

et al. discuss the advances made in the art but also indicate that more progress needs to be made in the art. In the conclusion of their review, Jen et al. assert, "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has remained elusive." It is also stated "The key challenges to this field have been outlined above. It is clear that they will have to be solved if this approach to specific antitumor therapy is to become a useful treatment approach. A large number of diverse and talented groups are working on this problem, and we can all hope that their efforts will help lead to establishment of this promising form of therapy." It is clear from Jen et al. that the state of the art of antisense is unpredictable and those highly skilled in the art are working towards making the art of antisense therapy more predictable but have many obstacles to overcome.

It would appear that in view of the above, one of ordinary skill in the art would require specific guidance on how to practice the current invention. The current specification does not provide such guidance and one of ordinary skill in the art would be required to perform undue trail and error experimentation to practice the current invention. The quantity of undue experimentation would include overcoming the obstacle to routine antisense therapies as exemplified in the references discussed above. In addition, the quantity of undue experimentation would include the modes of treatment selected from the range of diseases contemplated (e.g. hyperproliferative disorders and cancer), for example.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Schneider (Forschungszentrum Karlsruhe, 2001, FZKA 6587, 1-139). (Please note, translation will be provided as it becomes available).

Claim 1 is drawn to a compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding thyroid hormone receptor interactor 6 (SEQ ID NO:3) which specifically hybridizes with and inhibits the expression of thyroid hormone receptor interactor 6. Claim 2 is drawn to the compound of claim 1 which is an antisense oligonucleotide. Claim 11 is drawn to a compound 8 to 50 nucleobases in length which specifically hybridizes with at least an 8-nucleobase portion of an active site on a nucleic acid molecule encoding thyroid hormone receptor interactor 6.

Schneider discloses the reduction of endogenous thyroid hormone receptor interactor 6 (Trip6) protein by antisense techniques (see Abstract). Schneider further discloses a reverse PCR oligonucleotide primer of 27 nucleobases in length (see page 41, $Trip_{rev}$). Since this oligonucleotide is 100% complementary to thyroid hormone receptor interactor 6, it is assumed that the oligonucleotide inherently possesses antisense activity.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2 and 4-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schneider (Forschungszentrum Karlsruhe, 2001, FZKA 6587, 1-139) in further view of Baracchini et al. [U.S. Patent No. 5801154] and Fritz et al. (Journal of Colloid and Interface Science, 1997 Vol. 195:272-288).

Claims 1, 2 and 4-14 are drawn to a compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding thyroid hormone receptor interactor 6; wherein said compound specifically hybridizes with said nucleic acid molecule encoding thyroid hormone receptor interactor 6 and inhibits the expression of thyroid hormone receptor interactor 6; wherein the compound is an antisense; wherein the antisense oligonucleotides comprises at least one modified internucleoside linkage; wherein the modified internucleoside linkage is a phosphorothioate linkage; wherein the antisense oligonucleotide comprises at least one modified sugar moiety; wherein the sugar moiety is a 2'-O-methoxyethyl sugar moiety; wherein the antisense oligonucleotide comprises at least one modified nucleobase; wherein the modified nucleobase is a 5-methylcytosine; wherein the antisense oligonucleotide is a chimeric oligonucleotide; and a composition comprising the compound of claim 1 and a pharmaceutically acceptable carrier or diluent, further comprising a colloidal dispersion system.

Schneider teach the reduction of endogenous thyroid hormone receptor interactor 6 (Trip6) protein by antisense techniques (see Abstract). Schneider further teach a reverse PCR oligonucleotide primer of 27 nucleobases in length (see page 41, $Trip_{rev}$). Since this oligonucleotide is 100% complementary to thyroid hormone receptor interactor 6, it is assumed that the oligonucleotide inherently possesses antisense activity.

Schneider does not teach an antisense oligonucleotide wherein the antisense oligonucleotides comprises at least one modified internucleoside linkage; wherein the modified internucleoside linkage is a phosphorothioate linkage; wherein the antisense oligonucleotide comprises at least one modified sugar moiety; wherein the sugar moiety is a 2'-O-methoxyethyl sugar moiety; wherein the antisense oligonucleotide comprises at least one modified nucleobase; wherein the modified nucleobase is a 5-methylcytosine; wherein the antisense oligonucleotide is a chimeric oligonucleotide; and a composition comprising the compound of claim 1 and a pharmaceutically acceptable carrier or diluent, further comprising a colloidal dispersion system.

Baracchini et al. teach modified or substituted oligonucleotides are often preferred over native forms because of desirable properties such as enhanced cellular uptake, enhanced affinity for nucleic acid target and increased stability in the presence of nucleases. Baracchini et al. further teach antisense oligonucleotides with phosphorothioate modified backbones (see column 6, line 37)... with at least one modified sugar moiety and a modified 2'-O-methoxyethyl sugar moieties (see Table I)... with modified nucleobases, such as 5-methylcytosine (see column 7, lines 15-25). Baracchini et al. finally teach an antisense oligonucleotide as a chimeric oligonucleotide (see column 8, lines 12-19)

Fritz et al. teach a composition comprising an antisense oligonucleotide and a pharmaceutically acceptable carrier or diluent comprising a colloidal dispersion system. Fritz et al. further teach that oligonucleotides, in combination with steric stabilizers, exhibit high colloidal stability with low toxic side effects as required for biological experiments in cell culture and *in vivo* (see page 287, last paragraph).

It would have been obvious to make antisense oligonucleotides encoding thyroid hormone receptor interactor 6 (Trip6) since the prior art has asserted that it is of considerable interest to investigate the possible role of Trip6 in human cancers (Yi and Beckerle). One of ordinary skill in the art would have had a reasonable expectation of success in making antisense oligonucleotides targeting thyroid hormone receptor interactor 6 since Schneider taught the reduction of endogenous Trip6 protein by antisense techniques. One of ordinary skill in the art would have been motivated to modify antisense oligonucleotides since the prior art has taught the desirability of such oligonucleotides are often preferred over native forms because of enhanced cellular uptake, enhanced affinity for nucleic acid target, increased stability in the presence of nucleases and the exhibition of high colloidal stability with low toxic side effects as required for biological experiments (Baracchini et al. and Fritz et al.).

The invention as a whole would therefore have been obvious to one of ordinary skill in the art at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (703) 306-3221. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 746-8693 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

tcg
September 9, 2002

SEAN McGARRY
PRIMARY EXAMINER
1635